

## **BPCA Executive Summary**

NDA 20-241/S-032 Lamictal (lamotrigine) Tablets

NDA 20-764/S-025 Lamictal (lamotrigine) Chewable Dispersible Tablets

FROM: Division of Neurology Products (DNP)

SUBJECT: Adjunctive Therapy in Partial Seizures, Patients 1-24 Months

## **BPCA Clinical Summary**

The sponsor has submitted the results of Study LAM20006 in response to a Pediatric Written Request.

Lamictal is already approved as adjunctive therapy for partial seizures in adults and in pediatric patients 2 years of age and older. To support the extension of the claim in labeling down to 1 month of age, the sponsor conducted a single controlled trial, LAM20006.

## **Study LAM20006**

LAM20006 was a randomized, double-blind, placebo-controlled parallel-group study. It followed an enrichment design. Patients were first enrolled in an open-label period. Lamictal was added on to existing therapy (patients could be taking 1-2 concomitant AEDs) and seizure diary data was collected. Patients who demonstrated a protocol-specified percent reduction in seizures during this phase were eligible to be randomized to 1) continue Lamictal, or 2) undergo a gradual withdrawal to placebo. The withdrawal occurred over 3 weeks with a 25% reduction in dose each week (75%, 50%, 25%, then discontinue). The double-blind phase that followed lasted 8 weeks.

As originally designed, the inclusion criteria required that patients demonstrate a 40-80% reduction in seizures during the open-label phase. A protocol amendment allowed that patients with a 40-100% reduction be enrolled. The sponsor argued that this was essential because it would make it more likely to show a treatment effect (larger between group difference) with a smaller sample size. Recruitment had been a problem early in the conduct of the study and the sponsor believed completion of the study was becoming impossible. Note that this amendment allowed patients to enter the double-blind phase who had 0 seizures during the last 4 weeks prior to randomization. These later infants would need only a single seizure to qualify for escape during the double-blind phase (see the next paragraph).

The primary outcome was the proportion of patients in each randomized group who met any of the following failure criteria over the course of the study. A secondary outcome was an analysis of the time-to-failure. The failure criteria were:

1. 50% increase in monthly seizure frequency compared to the seizure frequency during the last 4 weeks prior to randomization;
2. Doubling of the highest consecutive 2-day partial seizure count observed during the last 4 weeks prior to randomization;
3. Onset of a new and more severe seizure type;
4. Clinically significant worsening of non-partial seizures;
5. The need to use any therapeutic intervention to control seizures;
6. Status epilepticus.

Patients were dosed based on concomitant AEDs. There were 2 groups: 1) those on enzyme-inducing AEDs (EIAEDs), and 2) those on VPA or neutral AEDs. [Note that this dosing paradigm differs from current labeling for adults and pediatric patients older than 2 years of age that has 3 different dosing groups: 1) EIAEDs, 2) VPA, and 3) non-EIAEDs and no VPA.] Patients were not allowed to be on a combination of concomitant AEDs that included both VPA and an EIAED.

The original sample size estimate called for 60 infants to be randomized. However, the planned sample size was later reduced by protocol amendment to 38. This was based on: 1) the better-than-expected responses seen during the open-label enrichment phase, 2) the revised inclusion criteria for the double-blind phase that allowed patients with 80-100% reductions in seizures during the enrichment phase (in addition to patients with 40-80% reductions) to be randomized. The sponsor believed that, without these changes, it would be impossible to complete the study in a reasonable timeframe.

A total of 38 subjects were randomized, 19 to Lamictal and 19 to placebo.

### **Baseline Demographics**

The ages of enrolled patients were as follows:

< 6 months	1
6-12 months	14
> 12 months	23

The presenting seizure types were:

Simple partial	12	
Complex partial		26
Secondarily generalized		13
Generalized seizures	11	

Concomitant AED group for dosing purposes:

Induced	27
Non-induced	11

The baseline seizure counts during the last 4 weeks of the open-label period are shown below:

Lamictal	Placebo
0	0
0	0
2	0
2	0
3	0
3	0
7	0
9	1
11	1
12	1
16	4
26	6
37	13
40	15
41	16
46	51
55	157
73	165
103	179

Note that 9 of 38 patients had 0 seizures during the baseline phase. For those patients, a single seizure post-randomization would have satisfied the first failure criterion.

## Results

### *Sponsor Analysis*

The results of the protocol-specified analysis are shown below:

Lamictal		Placebo		p-value, chi-square test
N	Failures	N	Failures	
19	11 (58%)	19	16 (84%)	<b>0.074</b>

In the above analysis, patients who did not meet a failure criterion, but left the trial prematurely, were counted as failures as per the protocol. There were 2 such patients, both in the Lamictal group. In the original submission of this application, the reason given for the premature discontinuation of each of these patients was “protocol violation.”

The p-value from the logrank test for the time to failure is 0.059, again having counted the 2 Lamictal patients who prematurely discontinued as meeting failure criteria at the time of discontinuation.

### *FDA Analysis*

During this review period, the sponsor was asked to further clarify the “protocol violations” for the 2 Lamictal patients described above. Both patients were treated at the site in Turkey. For patient 6333, the sponsor responded that the patient was accidentally rolled over into the open-label extension trial and, by the time the mistake was recognized, it was too late to return the patient to double-blind treatment. For patient 6336, the sponsor responded that the patient had actually met an exit criterion.

Having clarified the status of these 2 patients, the protocol-specified analyses remain unchanged since the protocol stated that such discontinued patients should be treated as failures. Dr. Yan obtained the same result as the sponsor on the primary analysis (proportion of failures), but a different p-value for the logrank analysis (**0.067 versus 0.059**) because she found that a Lamictal patient had an earlier exit date than the one the sponsor used in the analysis. (The sponsor had used the last day of dosing versus the day of meeting the exit criterion.)

However, Dr. Yan repeated the time-to-failure analysis, treating patient 6333 as a censored patient (not a failure) and patient 6336 as a failure. This is a very reasonable approach. The p-value from the logrank test for this analysis is **0.051**.

## *Quality of the Data and Electronic Datasets*

During DNP's review, a number of questions were raised about the electronic datasets that still require further clarification from the sponsor.

## **Conclusions**

At the conclusion of the review, DNP was unable to determine that lamotrigine is safe and effective for treating partial seizures in patients 1-24 months of age. Consequently, the sponsor was sent a not approvable letter. However, DNP believes that it may be possible to ultimately approve the application if the sponsor can adequately address a number of concerns.

### *A. Effectiveness*

Although protocol-specified analyses of Study LAM20006 failed to detect a statistically significant between-treatment difference, the p-values achieved were near the required 0.05, and there was clear numerical superiority in favor of Lamictal in both the proportion of patients meeting exit criteria and time to meeting exit criteria. It is possible that the lack of statistical significance was a result of the very small sample size enrolled in this trial. Given this possibility, as well as the fact of Lamictal's demonstrated effectiveness in older populations, DNP believes it might be possible to further analyze this trial to determine if, in fact, the trial could provide convincing evidence of Lamictal's effectiveness in this population. However, before this could be attempted, the sponsor will need to address the following specific concerns.

The sponsor allowed patients with a zero weekly seizure rate (i.e. 0 partial seizures in 4 weeks) during the "baseline" (i.e., terminal OLP) to be randomized without stratification for this variable. Because one of the failure criteria was a 50% increase in partial seizures during the double-blind phase, the randomized patients with no partial seizures during this baseline could meet an exit criterion at the time of a first seizure. The occurrence of a single seizure is an unusual failure criterion for patients who would have been considered refractory just prior to the enrichment phase of the study. Some of these patients had experienced more than 4 partial seizures *per day* during the historical lead-in phase, making it highly likely that they would meet the exit criterion over the course of the 8 week double-blind phase (and 7 of 9 such patients did fail).

Although DNP would not necessarily consider the enrollment of such patients a fatal flaw in the study, DNP believes this fact may have caused a bias in the study.

Specifically, there was a failure of the randomization with respect to these patients (2 in the Lamictal group and 7 in the placebo group). This unequal distribution would be expected to favor the Lamictal group because all these patients were more likely to meet an exit criterion (and 7 of the 9 did fail).

Secondly, this group of patients with no baseline seizures made up almost a fourth of the patients randomized, thereby heavily impacting the overall study results.

Although it is not immediately obvious how this potential bias may be addressed, the sponsor was asked to propose an approach that they believe will mitigate DNP's concerns (perhaps, for example, by proposing several possible alternative exit criteria for these patients).

If the sponsor is able to successfully address this issue, they will then need to address a number of additional questions that were raised during the review.

#### *B. Data and Electronic Datasets*

During DNP's review, a number of questions were raised about the electronic datasets.

To begin, there is a dataset listing exit criteria for 46 patients when only 38 patients were randomized. The sponsor was asked to explain this discrepancy.

Other inconsistencies were also noted.

If the sponsor is able to adequately address these concerns, DNP believes it might be possible to perform the following PK/PD analyses, which might be useful in further considering the results of the study.

#### *C. PK/PD Modeling*

Pharmacokinetic/pharmacodynamic (PK/PD) modeling may strengthen the argument that Lamictal is effective for partial seizures in this age group. The sponsor was sent a number of suggestions regarding further exposure-response analyses.

#### *D. Safety*

The sponsor was also asked to address a number of questions about the coding of adverse event terms for the submitted studies. The sponsor was asked to reanalyze and summarize any recoded adverse event data. Suggestions for better characterizing the adverse event profile in this age group (unable to communicate symptoms) were provided to the sponsor, for example, lumping certain AE terms under specific behaviors such as: 1) irritability; 2) crying; 3) decreased feeding/eating; 4) difficulty sleeping; and 5) decreased crawling/walking.

## **BPCA Clinical Pharmacology Summary**

### *Recommendations*

We have reviewed the pharmacokinetic data from Studies LAM20006 and LAM20007 and the population PK analysis that evaluated the efficacy and safety of LAMICTAL in pediatric patients (1-24 months of age) with partial seizures. These studies were conducted to fulfill a Pediatric Written Request (WR).

### Recommendation

No attempts were made to explore the relationship between the exposure and the pharmacodynamic response. Such an analysis would have provided more insights regarding the effectiveness of Lamictal in the present population (1 month – 24 months), especially given the fact that the primary analysis did not reach pre-specified statistical significance.

If this indication is approved, OCP recommends that the dosing should be based on the doses used in the clinical study, rather than the current approved dose in older children, unless other considerations become available to otherwise guide dosing. There is currently no information to support the need for increases in the dose for children on concomitant “neutral” antiepileptic drugs (AEDs), and the Sponsor has not evaluated whether those on enzyme inducing AEDs (EIAEDs) also require higher exposure. Exposure-response analysis of the data in LAM20006 and LAM20007 may be helpful in guiding dosage recommendations. If it is necessary to have specific doses for children < 2 y.o., then the dosing section should be carefully reviewed by the Agency and the Sponsor to minimize the risk of confusion in this complicated section of the labeling.

The dissolution comparisons of the clinical trial material and the marketed product should be provided and reviewed prior to approval. This should be referred to the Office of New Drug Quality Assessment.

OCP recommends several changes to the labeling. Satisfactory agreement must be reached between the Sponsor and the Agency regarding labeling. If lamotrigine will not have an indication in children < 2 y.o., the PK results in this population should not be described in the labeling.

### *Summary of Clinical Pharmacology and Biopharmaceutics Findings*

This supplement to NDA 20241 (S032) and 20764 (S025) was submitted to provide final study reports in fulfillment of the Pediatric Written Request originally issued on December 17, 1998 and modified on July 3, 2000 to study lamotrigine as adjunctive treatment of partial seizures in patients age 1 month to 2 years of age. The submission date for exclusivity was extended to December 1, 2006.

The following studies were stipulated by the Written Request (WR) for lamotrigine:

- Study 1: An open-label lead-in phase, followed by a double-blind, placebo-controlled, randomized, add-on phase assessing the efficacy, safety, and pharmacokinetics of LAMICTAL in pediatric patients (1-24 months of age) with partial seizures. “Standard” PK parameters were to be determined.
- Study 2: An open, uncontrolled, long-term safety study of lamotrigine as add-on therapy in pediatric patients 1 month to 2 years of age with partial seizures.

Studies 1 and 2 in the WR were addressed by Studies LAM 20006 and LAM 20007, respectively. The key findings with respect to the conduct of the PK study and the Clinical Pharmacology of lamotrigine in the pediatric population age 1 month to 2 years of age are as follows:

- Subjects were reasonably distributed across age groups of  $\geq 6$ - $\leq 12$  months or  $> 12$  months old. In study 1 there was only 1 child  $< 6$  months old, and in Study 2 there were 16 subjects  $< 6$  months old. The youngest child in the PK population was 2.4 months old.
- The lamotrigine doses used in the study were titrated up to a maintenance dose. The dosing regimens were on a mg/kg basis. Subjects taking concomitant valproic acid (VPA) or non-enzyme inducing antiepileptic drugs (non-EIAEDs or “neutrals”) received the same dose and subjects taking concomitant EIAEDs received a higher dose.
- The population mean estimate of clearance of lamotrigine in pediatric patients 2 to 26 months of age, weighing 3 to 16 kg was 1.27 to 2.16 mL/min/kg in patients taking carbamazepine, phenytoin, phenobarbital, or primidone; 0.21 to 0.36 mL/min/kg in patients taking valproate; 0.70 to 2.07 mL/min/kg in patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate
- Clearance was greater in the neutrals and subjects taking EIAEDs than in patients taking VPA. Population PK analysis showed clearance in neutrals was intermediate between Clearance in patients taking EIAEDs and VPA. These data are in agreement with data from older children (historical controls) in the approved labeling. However, across all concomitant AED drug groups, the clearance is lower in the 2-24 month population than in 10 months to 5.3 y.o.
- The Sponsor is proposing that the dose of lamotrigine in neutrals be doubled to account for the increased clearance (as is the approved dose for older children). OCP does not believe this is acceptable for the following reasons:
  - Subjects taking neutral drugs or valproate concomitantly with lamotrigine were assigned to receive the same initial mg/kg doses, with mean total daily dose at the end of the OLP only 22% greater in neutrals than in valproic acid subjects in Study LAM20006. (Final dose was achieved by titration to what was considered to be the “optimal” dose). The mean average total daily lamotrigine dose for the neutral group was approximately 19% greater than that of the VPA group in Study LAM20007. The similarity of the final dose in the “neutral” group to the dose of the VPA subjects does not support a

justification for doubling the dose of LAMICTAL in the neutral group. However, if exposure response were to suggest that the dose in the “neutral” group should be further optimized, then it should be considered whether the dose in the EIAED group should also be optimized, since exposure in that group was approximately half that in the valproic acid group.

- Although median reduction in seizure count is not a primary efficacy endpoint in LAM20006, data for this measure available throughout the open label period (during titration to the optimal dose) does not suggest that “neutral” subjects had a lower response in this measure during the titration period, despite lower plasma concentrations than observed in the subjects with either valproic acid or EIAEDs.
  - There is no evidence to support which level of exposure (i.e. plasma concentrations achieved by “neutrals”, valproic acid, or inducer groups) is optimal and should be used as a reference for selecting a new dose for the “neutral” group.
  - There is little safety data to support the safety of increased doses/dose escalation in patients 1 month-24 months old. Increasing the dose in the absence of safety data in this population is contrary to the information in the approved LAMICTAL labeling that carries a boxed warning regarding the risk of serious skin rashes. It states that risk factors include exceeding recommended initial dose of LAMICTAL and exceeding recommended dose escalation of LAMICTAL.
- If Lamictal will not be indicated in the < 2 y.o. age group, the PK in this population should not be described in labeling.
  - The clinical trial formulation was not the same as the marketed product. The differences are due to the absence of commercial markings on the clinical trial material. As of 5/16/07 the Sponsor has not provided the requested dissolution comparisons of the clinical trial material and the marketed product.

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